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Life Sciences
working for a better future

Dr Damment,
Director of Preclinical,
Shire Pharmaceuticals Development,
East Anton,
Andover,
Hampshire,
SP10 5RG.

Dear Dr Damment,

REF: Final report for Huntingdon Life Sciences, Study Number: RBB 001

Please accept my apologies for the late delivery of this report but it was inadvertently sent to the original addressee at Roberts Pharmaceuticals Co Ltd in the US. Paul Smith the Study Director of this study, has now left Huntingdon Life Sciences therefore please address any further correspondence on this study to me.

Best regards,

C. J. Hardy.

Dr Colin J Hardy,
Principal Toxicologist,
Inhalation Studies Group.

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Huntingdon

METOCLOPRAMIDE

TOXICITY STUDY BY INTRANASAL ADMINISTRATION

TO CYNOMOLGUS MONKEYS FOR 13 WEEKS

METOCLOPRAMIDE

TOXICITY STUDY BY INTRANASAL ADMINISTRATION TO CYNOMOLGUS MONKEYS FOR 13 WEEKS

Sponsor

Roberts Pharmaceutical Corporation,
4 Industrial Way West,
Eatontown,
NJ 07724,
U.S.A.

Research Laboratory

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Report issued 24 May 2000

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TOXICOKINETICS DURING A TOXICITY STUDY BY INTRANASAL ADMINISTRATION TO CYNOMOLGUS MONKEYS FOR 13 WEEKS 171

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

The United Kingdom Good Laboratory Practice Regulations 1997, Statutory Instrument No. 654, and from 14 December 1999, The United Kingdom Good Laboratory Practice Regulations 1999, Statutory Instrument No. 3106

EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No L 77/8)

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.

United States Food and Drug Administration, Title 21 Code of Federal Regulations Part 58, Federal Register, 22 December 1978 and subsequent amendments.

The Study Director had no control over the unavailability of the expiry date of the test substance and hence no claim for compliance can be made in this respect.

....

Paul A. Smith, B.Sc. (Hons.),
Study Director,
Huntingdon Life Sciences Ltd.

Date

QUALITY ASSURANCE STATEMENT

The following inspections and audits have been carried out in relation to this study:

Study Phase	Date of Inspection	Date of Reporting
Protocol Audit		
Study Based Inspections		
Study Preparation	)	
Dosing Procedure	)	
Clinical Signs Recording	)	
Formulation Records	)	
Data Review	)	
Toxicokinetic Blood Sampling	)	
Bioanalytical Procedures		
Bioanalytical Procedures		
Dosing Procedure	)	
Formulation Records	)	
Clinical Signs Recording	)	
Bodyweights Recording	)	
Feeding & Food Consumption Records	)	
Data Review	)	
Blood Withdrawal Records	)	
Post Mortem	)	
Data Review	)	
Report Audit		

Protocol Audit: An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

Study based inspections: Inspections of phases of this study were conducted and reported to the Study Director and Company Management as indicated above.

Process based inspections: At or about the time this study was in progress inspections of other routine and repetitive procedures employed on this type of study were carried out. These were promptly reported to appropriate Company Management.

QUALITY ASSURANCE STATEMENT

(continued)

Report Audit: This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

.....

Andrew Gilbert,
Group Manager,
Department of Quality Assurance,
Huntingdon Life Sciences Ltd.

CONTRIBUTING SCIENTISTS

STUDY MANAGEMENT

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Principal Toxicologist,
Inhalation Studies Group.

Paul A. Smith, B.Sc. (Hons.),
Study Director,
Inhalation Studies Group.

Paul J. Horrell, B.Sc. (Hons),
Study Supervisor,
Inhalation Studies Group.

CLINICAL LABORATORY SERVICES

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Head, Department of Pharmacokinetics.

STATISTICS

Graham F. Healey, B.Sc., M.Sc., A.R.C.S.,
Head, Department of Statistics.

SUMMARY

The objective of the study was to assess and compare the systemic toxic potential of two formulations of metoclopramide spray during a 13-week intranasal study in cynomolgus monkeys.

Eighteen cynomolgus monkeys (9 males and 9 females) were used on the study. Three groups of monkeys (each of 3 males and 3 females) received metoclopramide nasal spray, metoclopramide menthol nasal spray or a placebo menthol spray (nominally 50 µl each spray) to one or both nostrils, up to 4 times per day.

The test animals received a variable dose for the first 3 weeks of the study. Thereafter the test animals received metoclopramide at a nominal dose of 80 mg/day (males) or 40 mg/day (females) except for one male and one female from Group 2 which received 20 mg/day of the metoclopramide nasal spray. Control animals received the equivalent dose volume.

Throughout the study the animals were observed daily for clinical signs. Bodyweights and food consumption were reported weekly. Selected parameters for haematology and biochemistry were measured pre-dose and during Week 13 of dosing. Selected parameters for haematology were also measured during Week 4. Plasma samples for toxicokinetic investigations were collected on Day 1 and during Week 13. Following 13 weeks of dosing, all animals were killed and subjected to a detailed macroscopic examination, selected organs were weighed and an extensive list of tissues was preserved from which selected tissues from all animals were examined microscopically.

The following comments in relation to the principal findings in the study are made in summary:

Clinical signs

Clinical signs related to the administration of metoclopramide were underactivity/lethargy, hunched/abnormal posture, body/limb tremors, loose/liquid faeces, closed or partially closed eyes, salivation and piloerection. Other clinical signs observed indicated central nervous system effects and included effects on posture, behaviour and orientation.

Bodyweight

There were no statistically significant differences between group means. However, slight bodyweight losses were observed among several metoclopramide treated animals during the first week of the study. In addition, two male animals (111M Group 2 and 121M Group 3) showed a slight, overall bodyweight loss during the study. Two Group 3 females (118F and 120F) showed only slight bodyweight gain compared with all other females.

Food consumption

Treated females showed a moderate reduction in food consumption compared to control.

Laboratory investigations

At Weeks 4 and 13 differences for some red cell parameters between the treated groups and control were related or possibly related to administration of metoclopramide. The differences in both treated groups comprised of a decrease in the haematocrit, haemoglobin concentration and red blood cell count (both sexes) and the mean cell haemoglobin concentration (males) when compared to control. The reticulocyte counts for both sexes of Group 2 showed a clear increase when compared to control at Weeks 4 and 13.

Toxicokinetics

The rate and extent of systemic exposure of male and female monkeys to metoclopramide on Day 1 and during Week 13 were higher after intranasal administration of metoclopramide nasal spray than after administration of metoclopramide menthol nasal spray although formal statistical significance was not reached.

Conclusion

It is concluded that intranasal administration of metoclopramide at doses of approximately 80 mg/day (males) or 40 mg/day (females) for 13 weeks caused clinical effects of which many were associated with the known adverse central nervous system effects of metoclopramide.

Plasma concentrations of metoclopramide were higher after administration of the metoclopramide nasal spray than after the metoclopramide menthol spray but there was no clear distinction in the response of the animals. The intranasal route revealed no evidence of local toxicity from either formulation.

INTRODUCTION

The purpose of this study performed at the Huntingdon Life Sciences Limited, Huntingdon Research Centre, Huntingdon, England, was to assess and compare the systemic toxic potential of two formulations of metoclopramide spray in cynomolgus monkeys *(Macaca fascicularis)* following intranasal administration for 13 weeks.

The study was not designed to meet any specific regulation or guidelines.

The test substance, metoclopramide, is an anti-emetic agent. The test substance was administered intranasally, an intended clinical route. The doses were selected in consultation with the Sponsor on the basis of the anticipated clinical dose. The cynomolgus monkey was the species of choice because the nasal architecture is similar to that of humans. In addition, the Sponsor has performed previous studies with this test substance in primates. The cynomolgus monkey is accepted as a predictor of toxic change in man and fulfils the requirement for a non-rodent species. The breed was selected on account of the availability of comprehensive background data.

RELEVANT STUDY DATES

Approval of protocol by:

Study Director
Huntingdon Life Sciences Management
Sponsor

Animals arrived at Huntingdon:

Treatment commenced:

Haematology & Biochemistry:

Pre-dose
Week 4 (Haematology only)
Week 13

Toxicokinetic blood sampling:

Week 1 (Day 1)
Week 13

Terminal kill: